Chemoprevention of Ultraviolet Radiation-induced Skin Cancer

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The use of chemical and physical sunscreening agents has increased dramatically during the last two to three decades as an effective means of preventing sunburn. The use of high sun-protection factor sunscreens has also been widely promoted for the prevention of skin cancer, including melanoma. Whereas sunscreens are undoubtedly effective in preventing sunburn, their efficacy in preventing skin cancer, especially melanoma, is currently under considerable debate. Sunscreens have been shown to prevent the induction of DNA damage that presumably results from the direct effects of ultraviolet radiation (UVR) on DNA. DNA damage has been identified as an initiator of skin cancer formation. However, both laboratory and epidemiological studies indicate that sunscreens may not block the initiation or promotion of melanoma formation. These studies suggest that the action spectrum for erythema induction is different than the action spectrum for the induction of melanoma. Indeed, recent reports on the wavelength dependency for the induction of melanoma in a fish model indicate that the efficacy of ultraviolet A wavelengths (320–400 nm) to induce melanoma is orders of magnitude higher than would be predicted from the induction of erythema in man or nonmelanoma skin tumors in mice. Other strategies for the chemoprevention of skin cancer have also been reported. Low levels and degree of unsaturation of dietary fats protect against UVR-induced skin cancer in mice and humans. Compounds with antioxidant activity, including green tea extracts (polyphenols), have been reported to inhibit UVR-induced skin carcinogenesis. — *Environ Health Perspect* 105(Suppl 4): 981–984 (1997)

Key words: ultraviolet radiation, skin cancer, chemoprevention, sunscreens, DNA damage, melanoma, erythema, immunosuppression

Solar ultraviolet radiation (UVR) induces a number of pathologic changes initiated in mammalian skin, including erythema, edema, hyperplasia, sunburn cell formation, immune suppression, and skin cancer. Chemical and physical screening agents have been developed over the last two decades for the prevention of sunburn and skin cancer. Sunscreens also prevent the induction of DNA damage. Dietary lipids and topically and orally administered antioxidants have been reported to reduce the formation of skin cancer and suppression of the immune system following exposure to UVR.

This paper is based on a presentation at the symposium on Mechanisms and Prevention of Environmentally Caused Cancers held 21–25 October 1995 in Santa Fe, New Mexico. Manuscript received at *EHP* 16 April 1996; accepted 23 August 1996.

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Abbreviations used: PABA, *p*-aminobenzoic acid; SPF, sun protection factor; UV-A, ultraviolet A (320–400 nm); UV-B, ultraviolet B (280–320 nm); UVR, ultraviolet radiation.

Sunscreening Agents

Skin Cancer

A number of studies have shown that sunscreens are effective in the prevention of UVR-induced skin cancers in mice (*1–6*). Evidence supporting the capacity of sunscreening agents to prevent UVR-induced skin cancers in humans is less extensive and, in the case of melanoma, is controversial. Daily application of sunscreens for 1 year (*7*) and 2 years (*8*) resulted in a significant decrease in the appearance of actinic keratoses, the putative precursor lesion for squamous cell carcinomas in humans. There appears to be no evidence to support the notion that use of sunscreens prevents the induction of melanoma in humans (*9–13*). In fact, Garland et al. (*14*) recently proposed that increased use of sunscreens that protect efficiently against ultraviolet B (UV-B), but not ultraviolet A (UV-A), is responsible, at least in part, for the increased incidence of melanoma. UV-B includes those wavelengths of UVR between 280 and 320 nm. UV-A includes those wavelengths of UVR between 320 and 400 nm. Garland and co-workers reason that the use of sunscreens that are very effective in preventing sunburn results in increased exposure to UV-A during extended hours spent outdoors. This hypothesis would require that the action spectrum for melanoma induction deviate from the action spectrum for sunburn formation. If these action spectra were the same, sunscreens protective against sunburn would be equally protective against melanoma (*15*). An action spectrum is the relative response of a system to different wavelengths of radiation.

Setlow et al. (*16*) have determined an action spectrum for the induction of melanoma in a fish model. They reported that melanomas were readily induced at 365, 405, and probably 436 nm—wavelengths of UV-A and visible radiation that are not strongly absorbed by DNA. However, melanomas that develop in the fish may arise from atypical melanocytes and may not be equivalent to human melanoma. The relative sensitivities for melanoma induction in fish at these wavelengths were several orders of magnitude greater than the sensitivities for erythema induction in humans by the same wavelengths. Setlow et al. (*16*) conclude that the general shape of the action spectrum for transforming fish melanocytes should be the same for transforming mammalian melanocytes. Based on this action spectrum, Setlow and colleagues have calculated that 90 to 95% of human melanoma induction by natural sunlight may be caused by wavelengths > 320 nm. Thus, use of conventional sunscreens would be ineffective in preventing melanoma and the use of such screens could result in an increased exposure to melanoma-inducing wavelengths (*17*). Increased exposure to melanoma-inducing wavelengths could also result from the use of artificial tanning devices. Devices currently used for tanning emit mainly UV-A radiation at intensities capable of stimulating pigmentation following relatively short exposure times (< 60 min). The results of studies to date have been inconsistent in defining an association between the use of tanning devices emitting UV-A radiation and malignant melanoma (*18–22*). However, results from a recent study in Sweden indicate a causal relationship between the use of tanning devices and malignant melanoma, especially in individuals under the age of 30 (*23*). A small dose response was evident in

this study. Individuals who used sunbeds or sunlamps more than 10 times per year had a higher risk for malignant melanoma than those individuals who were exposed 1 to 10 times per year.

Although the factors that influence the induction of melanoma appear more complex than those involved in the induction of nonmelanoma skin cancer, the bulk of evidence supports the hypothesis that the recent increase in melanoma is related to increased exposure to UVR and that this may be the result of exposure to UV-A rather than UV-B wavelengths. It has been estimated that at least 65% of the melanomas that occurred worldwide in 1985 were caused by solar exposure (*24*).

DNA Damage

DNA damage, particularly the cyclobutane pyrimidine dimer, has been implicated as the initiating event for UVR-induced tumorigenesis. Photoreactivation repair, a light-dependent repair pathway specific for dimerized pyrimidines, reportedly prevents UVR-induced tumorigenesis in fish (*25,26*) and opossums (*27,28*). Similarly, topical application of a DNA excision repair enzyme stimulates the repair of pyrimidine dimers (*29*) and delays the onset of UVR-induced skin tumors (*29,30*) in mice. Sunscreening agents reportedly prevent the induction of pyrimidine dimers in murine and human epidermal DNA. Suzuki (*31*) observed little or no protection from DNA damage with topical application of *p*-aminobenzoic acid (PABA) (1%) and urocanic acid (1%), but titanium dioxide at 1 and 5% appeared to provide 100% protection. A sunscreen formulation with a sun protection factor (SPF) of 15 reduced the induction of pyrimidine dimers in sunscreen-treated skin by a factor of approximately 50 upon exposure to solar-simulated radiation (*32*). Treatment of human skin with an SPF 10 sunscreen was reported to provide "excellent" protection against the induction of thymine dimers (*33*). PABA (8%), 2-ethylhexyl-*p*-methoxycinnamate (7.5%), and benzophenone-3 (6%) were determined to have SPFs of ≥8, ≥8, and ≥4, respectively, and to suppress the induction of DNA damage by 91, 86, and 67%, respectively (*34*).

Dietary Lipids

A number of studies have implicated dietary fat in the induction and development of tumors of various organs, including the skin. As early as 1939, Baumann and Rusch (*35*) observed that animals fed high-fat diets were more susceptible to UVR-induced skin tumors than animals on low-fat diets. This study was not well controlled, and it was not until 1983 that a carefully controlled nutritional study of the relationship of dietary lipids to UVR carcinogenesis was published (*36*). In this study, animals receiving hydrogenated corn oil demonstrated a significantly greater tumor latency period and fewer tumors per animal than those animals receiving comparable levels of unsaturated corn oil. Similarly, a series of studies carried out by Reeve and co-workers (*37*) showed that mice fed 20% saturated fat were almost completely protected from UVR carcinogenesis, compared to animals on a 20% unsaturated fat diet. Furthermore, when saturated fat-fed mice were exposed to UVR and then subsequently fed a diet containing unsaturated fat, multiple latent tumors appeared. The authors interpreted these results to mean that tumors initiated by UVR remained latent in the epidermis and were not expressed until the amount of unsaturated fat in the diet increased.

Black et al. (*38*) later demonstrated a near linear relationship between lipid level intake and tumor latency, i.e., tumor latency decreased with increases in lipid intake. Furthermore, increasing lipid intake was accompanied by an increase in numbers of tumors per animal. The influence of dietary lipids on susceptibility to photocarcinogenesis appears to involve more than level of lipid intake and degree of fatty acid unsaturation. Menhaden oil, an *n*-3 polyunsaturated fatty acid, significantly inhibited photocarcinogenesis in mice when compared to an equivalent level of *n*-6 fatty acid (*39*).

We recently used the opossum UVR/carcinogenesis model to investigate the role of dietary fat in susceptibility to UVR-induced melanoma. Four groups of age-, sex-, and litter-mate-matched opossums maintained on four diets containing varying levels and types of fat were exposed 3 times per week to suberythemal doses of UVR. Animals were scored for the appearance of melanotic skin tumors, nonmelanoma skin tumors, and corneal tumors. The fat composition of the four isocaloric diets were: diet 1, 3.5% corn oil (polyunsaturated fat); diet 2, 7% corn oil; diet 3, 14% corn oil; and diet 4, 14% lard (saturated fat). No significant differences were observed among the four groups in the time to appearance of nonmelanoma skin tumors or corneal tumors. However, the influence of dietary fat on susceptibility to UVR-induced melanotic tumors was dramatic. No UVR-induced melanotic tumors were observed in animals maintained on a saturated fat (lard) diet. The development of UVR-induced melanotic lesions was similar in animals maintained on the three corn oil diets.

Black and co-workers recently reported that a 2-year, low-fat intervention regimen resulted in a significant reduction in the occurrence of actinic keratosis (*40*) and nonmelanoma skin cancer (*41*) in individuals who had had a previous nonmelanoma skin cancer.

Although the precise mechanisms by which dietary lipids influence the photocarcinogenic process remain unknown, lipid peroxidation and modulation of the immune system may be involved.

Antioxidants

A number of compounds with antioxidant properties also have been shown to be anticarcinogenic. Of four selected phenols, butylated hydroxytoluene and vanillin significantly inhibited UVR carcinogenesis in mice (*42*). Two closely related phenols, butylated hydroxyanisole and propyl gallate, had no effect on the photocarcinogenic process (*42*).

Green tea extracts reportedly inhibit UVR-induced skin cancer in mice when applied topically or orally (*43–45*). The polyphenolic epicatechin and epicatechin derivatives are thought to be the ingredients in green tea extracts responsible for decreased susceptibility to UVR-induced tumorigenesis (*46*).

Ascorbic acid (*47*), β-carotene (*48*), α-tocopherol (*49*), and selenium (*50*) have exhibited antiphotocarcinogenic activities, possibly due to their antioxidant properties.

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